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Drugs in Clinical Use Which Cause Cancer

ROBERT HOOVER, M.D., and JOSEPH F. FRAUMENI, JR., M.D. Bethesda, Md.

IDENTIFICATION of chemical agents that cause cancer has come largely from studies in laboratory animals and surveys of industrial workers. In contrast, only limited information is available on drugs as carcinogens in man. This paper attempts to summarize the small amount of epidemiologic evidence for the carcinogenicity of drugs that have been, or are, in clinical use. However, the few agents implicated do not mean that other drugs in clinical practice do not cause cancer; instead, it indicates that the long-term effects of most drugs have simply not been assessed in man. Indeed, epidemiologic evaluation is urgent for widely used drugs that show clinical suspicion of a hazard or that are carcinogenic in the laboratory.

A classification of drug–cancer relationships in laboratory animals and man is shown in Table I. We shall present some criteria for selecting from these categories those drugs which should be evaluated in man.

Drug Exposures Associated with Human Cancer

This category, recently reviewed by Fraumeni and Miller,[1] is summarized in Table II. Some agents have been discontinued from clinical use at the recognition of carcinogenic potential. Others are still used because current estimates of the cost–benefit ratio warrant their administration in certain diseases. However, as different conditions are added to the therapeutic indications for a drug, new assessments of cost–benefit ratios must be made.

Radioisotopes exert carcinogenic effects by release of ionizing radiation at deposition sites in the body. For example, radioactive phosphorus increases the risk of leukemia in patients with polycythemia vera.[2] Radium and mesothorium, bone-seeking isotopes once used for various illnesses, produced a high rate of osteogenic sarcoma and carcinoma in mucous membranes near bone, such as the paranasal sinuses.[3] The same effect resulted from occupational exposures among radium-dial painters and radium chemists. Thorotrast, deposited in the reticuloendothelial system after use in radiographic studies, induced hepatic hemangioendotheliomas in many cases.[4]

Immunosuppressive agents (antimetabolites, corticosteroids, antilymphocyte serum) are suspected as being contributing factors to the high cancer risk experienced by renal transplant recipients. The mechanism undoubtedly involves some alteration of immunologic processes rather than chemical induction of malignant change. In a recent follow-up study of over 6000 recipients of renal transplants, the risk of lymphoma was about 35 times normal expectation—derived almost entirely from a risk of reticulum cell sarcoma that was 350 times higher than expected.[5] Skin and lip cancers occurred up to four times more often than expected, whereas the risk of other cancers showed a 2½-fold excess in men only, due

From the Epidemiology Branch, National Cancer Institute, Bethesda, Md. 20014.

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TABLE I

Categories of Drug-Cancer Relationships in Man and in Laboratory Animals

I. Drug exposures associated with cancer in man.

II. Drug exposures carcinogenic in laboratory animals that with investigation have thus far demonstrated no carcinogenicity for man.

III. Drug exposures carcinogenic in laboratory animals that have not been evaluated in man.

IV. Drug exposures either not carcinogenic in laboratory animals or whose carcinogenicity is unknown.

largely to soft tissue sarcoma and hepatobiliary carcinoma.

Since persons with heritable immunedeficiency syndromes are susceptible to lymphoma and possibly other cancers,[6] it is likely that immunosuppressive drugs play a role in post-transplant carcinogenesis. While there have been case reports of cancers developing in patients with other conditions treated with these drugs, as yet there has been no study to determine whether there is any real excess of malignancy. Perhaps the predisposition to neoplasia in transplant recipients results from an interaction between immunosuppression and immunostimulation by antigens from the grafted kidney. The mechanism will be important to establish. For while the cancer risk involved is currently considered acceptable for renal transplantation, similar risks involved in the use of the agents for less serious conditions might be unacceptable.

Cytotoxic agents used in cancer chemotherapy are often carcinogenic in laboratory animals, and some may induce cancer in man.[7] Chlornaphazine was withdrawn in 1964 when high doses for polycythemia vera and Hodgkin's disease were found to cause bladder tumors.[8] This drug is a derivative of β-naphthylamine, which was known to be a bladder carcinogen in industrial workers. In addition, certain alkylating agents seem to elevate the risk of acute leukemia, especially the myelocytic and monomyelocytic types. Most striking has been an increase in leukemia among patients with multiple myeloma treated with melphalan or cyclophosphamide,[9] although one cannot yet exclude the possibility that improved survival has permitted the development of a hematopoietic neoplasm related to the origin or natural history of myeloma. Another effect of cytotoxic drugs was suggested by a recent follow-up study of Hodgkin's disease, which showed that intensive chemotherapy enhanced the risk of second cancers originating at heavily irradiated sites.[10]

Synthetic estrogens, particularly stilbestrol, have triggered much recent concern about the carcinogenic effects of drugs. First evidence for a human transplacental carcinogen came in 1971, when a link was reported between stilbestrol and a cluster of vaginal adenocarcinoma in Boston among eight women between 14 and 22 years of age.[11] At present prenatal exposure to synthetic estrogens has been linked to clear cell carcinomas of the vagina and cervix in dozens of patients 7 to 25 years of age.[12] However, based on a recent follow-up study, the attack rate for these cancers following in utero exposure to estrogens has been estimated[13] thus far to be no greater than 4 per 1000.

Synthetic estrogens given after birth may also induce cancer. In a recent study of 24 patients receiving stilbestrol at least five years for gonadal dysgenesis, endometrial carcinoma developed in two and possibly three cases.[14] Together with three cases in the literature, the tumors were diagnosed between 28 and 35 years of age, and most were of an unusual mixed or adenosquamous type.

Exogenous androgens have been implicated in a recent series of eight patients with hepatocellular carcinoma following

TABLE II

Cancers Related to Drug Exposures in Man

Radioisotopes	
Phosphorus (^{32}P)	Acute leukemia
Radium, mesothorium	Osteosarcoma and sinus carcinoma
Thorotrast	Hemangioendothelioma of liver
Immunosuppressive Drugs (for renal transplantation)	
Antilymphocyte serum	Reticulum cell sarcoma
Antimetabolites	(?) Other cancers (skin, liver, soft tissue sarcoma)
Corticosteroids	
Cytotoxic Drugs	
Chlornapnazine	Bladder cancer
Melphalan	Acute myelomonocytic leukemia
Cyclophosphamide	
Hormones	
Synthetic estrogens	
prenatal	Vaginal and cervical adenocarcinoma (clear cell type)
postnatal	Endometrial carcinoma (adenosquamous type)
Androgenic-anabolic steroids (for aplastic anemia)	Hepatocellular carcinoma
Others	
Arsenic	Skin cancer
Phenacetin-containing drugs	Renal pelvis carcinoma
? Diphenylhydantoin	Lymphoma
Coal tar ointments	Skin cancer
? Chloramphenicol	Leukemia
? Amphetamines	Hodgkin's disease

long-term treatment of aplastic or Fanconi's anemia with androgenic-anabolic steroids, primarily oxymetholone or methyltestosterone derivatives.[15] Additional cases have been reported and underscore the need for further evaluation of these compounds.

Inorganic arsenicals have not been shown to be carcinogenic in experimental animals. However, when taken internally, the agents are generally considered to cause skin cancer in man.[16,17] The skin cancers following arsenical use are characteristically multiple, involve unexposed parts of the body and unusual locations (e.g., palms of the hand), and are associated with arsenical pigmentation and hyperkeratosis. Instances of lung cancer and liver hemangioendothelioma have been attributed to medicinal arsenic, but these occurrences may not be in excess of expectation.[17,18]

Large doses of analgesic drugs containing phenacetin are a causal factor in chronic pyelonephritis and papillary necrosis. Reports from various countries indicate that patients with "analgesic nephropathy" are at high risk of developing transitional cell tumors of the renal pelvis.[19-21] Coal tar and creosote preparations (containing polycyclic hydrocarbons) have been reported to cause skin cancer in laboratory animals, in exposed workers, and in patients using these preparations.[22]

Three drugs have question marks associated with their carcinogenicity—diphenylhydantoin, chloramphenicol, and

amphetamines. While there is some human evidence of carcinogenicity, adequate epidemiologic testing has not been done. Dilantin occasionally induces lymphoid reactions that regress on cessation of therapy. Transformation of this state to malignant lymphoma has been reported in several patients.[23] The nature of this association remains to be defined, but recent evidence in man and laboratory animals suggests that the drug may predispose to lymphoma by its capacity to concurrently depress and stimulate immune responses.[24,25] It is obvious, however, from two separate studies[26,27] that if there is an excess risk, it is almost certainly of small magnitude and probably quite acceptable given the drug's efficacy in the treatment of epilepsy.

Chloramphenicol and other marrow-depressing drugs have been implicated, by case reports, in the development of leukemia.[28,29] A causal relationship would be consistent with the potential of leukemogens (radiation, benzene, alkylating agents) to produce aplastic anemia.[29,30] The production of chromosomal defects by chloramphenicol supports the possibility of a leukemia hazard, since such defects are seen in various conditions at high risk of leukemia.[29,30]

Recently, a case-control study revealed a six-fold excess among Hodgkin's disease patients in the prior history of amphetamine use, mainly for weight reduction.[31] With the problems involved in obtaining a reliable history of such drug usage, this relationship needs further investigation.

Drugs with Carcinogenic Potential in Laboratory Animals But No Demonstrated Carcinogenicity in Man

Exactly which drugs are placed in this category depends on how rigorous an evaluation is expected in order to fulfill the requirements of investigation in man. If one expects true analytic epidemiologic studies of reasonable numbers of exposed persons followed up adequately to assess a long-term effect, then the list may be reduced to two drugs—isoniazid[32] and the female sex hormones, including natural and artificial estrogens, progestins, and combinations of these.[33-36] This short list attests to the difficulties of doing appropriate evaluations in humans. In man, it is probable that evaluations of carcinogens will have to include factors such as age, latent period, and cocarcinogen exposures that complicate the assessment of carcinogenicity.

Age at exposure as a determinant of carcinogenic risk is illustrated by the association of industrial chemical exposures with bladder cancer (Table III).[37] As is illustrated here, the younger the worker at first exposure, the greater the risk. In this study, the excess risk was limited to those first exposed under age 26.

The long latent period between exposure to a carcinogen and manifestation of the cancer is perhaps the single most important obstacle to adequate evaluation. Even

TABLE III

Relative Risk of Bladder Cancer According to Age When Employment in a Hazardous Occupation Began*

	Age at starting					
	12-15 yrs	16-20 yrs	21-25 yrs	26-35 yrs	36+ yrs	Never
Relative risk	4.8	2.5	2.0	1.1	1.3	1.0

* Risk of bladder cancer relative to a risk of 1.0 for those never employed in a hazardous occupation. Data taken from Hoover and Cole.[37]

one of the most potent industrial carcinogens known, β-naphthylamine, involves an average latent period of 18 years following exposure.[38] In other industrial exposures, the average latent periods are 40 to 50 years.[37] The role of this factor in recognizing drug-induced cancer is illustrated by the apparent relation of alkylating agents to acute leukemia. In the 26 reported cases of leukemia complicating multiple myeloma to date, the average latent period was about 4½ years.[9] Since the primary indication for this therapy is a usually fatal malignancy, the identification of risk was dependent on following up a fairly large number of relatively long survivors.

Cocarcinogens may be as important in human carcinogenesis as they are in laboratory animals. It is known, for example, that asbestos workers who smoke cigarettes have eight times the risk of dying from lung cancer as cigarette smokers who do not work with asbestos, and 92 times the risk of men who neither work with asbestos nor smoke cigarettes.[39]

These three factors, and probably others, need to be considered in the evaluation of carcinogenic risks. If not taken into account, each variable can inhibit the recognition and interpretation of drug-associated cancers. Often, these variables not only act independently but also interact with each other. This interaction is illustrated by the capacity of stilbestrol to cause genital tract adenocarcinomas. Production of the neoplasms has apparently involved a specifically timed prenatal exposure (probably first trimester), a latent period usually over ten years, and possibly a concomitant surge of endogenous estrogens during puberty (acting as a promoting factor).

Because of the problems involved in adequate evaluations of drugs in man, how confident are we that the negative findings reported for isoniazid and oral contraceptives are adequate? We think the answer is, "not very." In the case of oral contraceptives, there have been two well-designed and well-executed analytic studies of the relationship to cancer of the breast, the site thought most likely to be at risk.[35,36] These studies found no increased cancer risk, but oral contraceptives have been licensed for use only since 1960, and in widespread use only since 1965. Thus, the latent period that has elapsed between exposure and the evaluation for disease has only been five to ten years for even the earliest of users.

Probably even more important for an adequate assessment of a drug–cancer relationship is a knowledge of the epidemiology of the cancer in question. An example for breast cancer is the protective effect of early first birth—a woman who has her first child while less than 18 years of age has one third the risk of breast cancer of a woman having her first child after the age of 35 years.[40] Perhaps, then, an adverse effect of steroid drugs might be restricted to, or at least more prominent in, those women using them in early reproductive life. In a recent survey of Boston-area women of predominantly middle and upper social class, it was shown that women who are entering the breast cancer age range have not used these agents in their early reproductive lives, simply because they did not have the opportunity to do so.[41] The exposure being studied in these women, therefore, may not be relevant to the effect of exposure at a younger, more susceptible age. These difficulties, coupled with recent reports of an increased risk of two different types of neoplasia in oral contraceptive users (focal nodular hyperplasia of the liver[42] and in situ cervical neoplasia[43]), generate some uneasiness about the results of future evaluations.

Other Drug Exposures

The last two categories in Table I concern drugs not yet evaluated in man. How-

ever, in assessing priorities for epidemiologic study of these drugs, it would seem prudent to weigh (a) relative carcinogenicity in the laboratory, along with (b) the magnitude of population exposure and various parameters of this exposure (e.g., age, length of treatment, reason for treatment). Table IV lists a few drugs that would qualify for epidemiologic study at the earliest opportunity. Others may choose a different priority for human investigations, and obviously the list should be much longer.

Various agents in cancer chemotherapy have shown considerable carcinogenic potential in the laboratory. These drugs have enabled some young people with cancer to survive long periods[44,45] and are being used in combination much earlier in the natural history of various malignancies. Furthermore, these agents are employed increasingly in nonmalignant conditions,[46,47] so that a major effort is now required to assess the long-term risks.

Laboratory research has raised concern about a group of drugs classed as tertiary amines. Experimentally, these agents in the presence of a large amount of nitrite and an appropriately acidic pH form highly carcinogenic nitrosamines.[48] In man, it has been suggested that these drugs may produce nitrosamines after interacting with dietary nitrites in an acid stomach. Widespread population exposure over many years, and chronic use by some people, dictate the need for epidemiologic evaluation. Study of chlorpromazine and other phenothiazines may be justified through an entirely different rationale. These agents are potent stimulators of prolactin release in females.[49] Since prolactin may be a risk factor in breast cancer, the risk of this neoplasm should be estimated among a group of women treated with heavy doses.

In addition, iron dextran is listed because of its carcinogenicity in animals, widespread usage, and some case reports of malignancies at the site of injection.[50,51]

TABLE IV

Some Drug Exposures Carcinogenic in Laboratory Animals That Have Not Been Evaluated in Man

Chemotherapeutic Agents
Tertiary Amines
aminopyrine
oxytetracycline
chlorpromazine
etc.
Iron Dextran

Conclusions

In this report, we have summarized (a) the evidence that certain drugs induce cancer in man; (b) the difficulties involved in making an adequate evaluation of cancer risk in persons exposed to suspected agents; and (c) some guidelines that might help in selecting drugs for epidemiologic investigation. At present, only sparse human data exist to resolve questions regarding the carcinogenic potential of many drugs, including some in general use for many years.

So far, none of the positive studies of drug-associated cancers in man has been inspired by laboratory clues. Indeed, many agents found to be carcinogenic in man were at the time untested, or tested with negative results, in animals. The clues have been supplied usually by alert clinicians, reporting that something unusual was happening to people and stirring more analytic investigations. Since this approach has been fruitful, we should obviously encourage the continued reporting of suspicious associations and prompt epidemiologic pursuit.

However, with the increasing exposure of our society to a large battery of pharmacologic agents, many taken by healthy individuals, some mechanism is needed for determining which drugs should be evalu-

ated in man, other than waiting for a risk large enough to become clinically obvious. With the advances in comparative physiology and laboratory carcinogenicity testing, it seems likely that at least some of these decisions can now be made on the basis of expertise provided by laboratory scientists and epidemiologists. However, a third party is also needed — a group familiar not only with the toxicology of drugs but with the pattern of clinical usage. How many people take a particular drug? For what reasons? With what other agents? What are the characteristics of these people? Are there exposed populations available that are large enough and have the potential for adequate follow-up so that meaningful evaluations can be made? The clinical pharmacologist can provide this necessary link in the informational system, and lines of communication with epidemiologists and experimentalists should be encouraged.

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